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(54) Title: IL-8 RECEPTOR ANTAGONISTS

(57) Abstract

This invention relates to novel phenyl ureas useful in the treatment of disease states mediated by the chemokine, Interleukin-8 (IL-8).

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IL-8 RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to a novel group of phenyl urea compounds, processes for the preparation thereof, the use thereof in treating IL-8, GROα, GROβ, GROγ, NAP-2, and ENA-78 mediated diseases and pharmaceutical compositions for use in such therapy.

BACKGROUND OF THE INVENTION

Many different names have been applied to Interleukin-8 (IL-8), such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor. Interleukin-8 is a chemoattractant for neutrophils, basophils, and a subset of T-cells. It is produced by a majority of nucleated cells including macrophages, fibroblasts, endothelial and epithelial cells exposed to TNF, IL-1α, IL-1β or LPS, and by neutrophils themselves when exposed to LPS or chemotactic factors such as FMLP. M. Baggiolini et al, J. Clin. Invest. *84*, 1045 (1989); J. Schroder et al. J. Immunol. *139*, 3474 (1987) and J. Immunol. 144, 2223 (1990) ; Strieter, et al. Science 243, 1467 (1989) and J. Biol. Chem. 264, 10621 (1989); Cassatella et al. J. Immunol. 148, 3216 (1992).

GROα, GROβ, GROγ and NAP-2 also belong to the chemokine α family. Like IL-8 these chemokines have also been referred to by different names. For instance GROα, β, γ have been referred to as MGSAα, β and γ respectively (Melanoma Growth Stimulating Activity), see Richmond et al, J. Cell Physiology 129, 375 (1986) and Chang et al, J. Immunol 148, 451 (1992). All of the chemokines of the α-family which possess the ELR motif directly preceding the CXC motif bind to the IL-8 B receptor.

IL-8, GROα, GROβ, GROγ, NAP-2 and ENA-78 stimulate a number of functions in vitro. They have all been shown to have chemoattractant properties for neutrophils, while IL-8 and GROα have demonstrated T-lymphocytes, and basophiles chemotactic activity. In addition IL-8 can induce histamine release from basophils from both normal and atopic individuals GRO-α and IL-8 can in addition, induce lysozomal enzyme release and respiratory burst from neutrophils. IL-8 has

also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis. This may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many known diseases are characterized by massive neutrophil infiltration. As IL-8, Groα, GROβ, GROγ and NAP-2 promote the accumulation and activation of neutrophils, these chemokines have been implicated in a wide range of acute and chronic inflammatory disorders including psoriasis and rheumatoid arthritis. Baggiolini et al, FEBS Lett. 307, 97 (1992); Miller et al, Crit. Rev. Immunol. 12, 17 (1992); Oppenheim et al. Annu. Rev. Immunol. 9, 617 (1991); Seitz et al., J. Clin. Invest. 87, 463 (1991); Miller et al., Am. Rev. Respir. Dis. 146, 427 (1992); Donnely et al., Lancet 341, 643 (1993). In addition the ELR chemokines (those containing the amino acids ELR motif just prior to the CXC motif) have also been implicated in angiostasis. Strieter et al., Science 258, 1798 (1992).

In vitro, IL-8, GROα, GROβ, GROγ, and NAP-2 induce neutrophil shape change, chemotaxis, granule release, and respiratory burst, by binding to and activating receptors of the seven-transmembrane, G-protein-linked family, in particular by binding to IL-8 receptors, most notably the B-receptor. Thomas et al., J. Biol. Chem. 266, 14839 (1991); and Holmes et al., Science 253, 1278 (1991). The development of non-peptide small molecule antagonists for members of this receptor family has precedent. For a review see R. Freidinger in: Progress in Drug Research, Vol. 40, pp. 33-98, Birkhauser Verlag, Basel 1993. Hence, the IL-8 receptor represents a promising target for the development of novel anti-inflammatory agents.

Two high affinity human IL-8 receptors (77% homology) have been characterized: IL-8Rα, which binds only IL-8 with high affinity, and IL-8Rβ, which has high affinity for IL-8 as well as for GRO-α, GROβ, GROγ and NAP-2. See Holmes et al., supra; Murphy et al., Science 253, 1280 (1991); Lee et al., J. Biol. Chem. 267, 16283 (1992); LaRosa et al., J. Biol. Chem. 267, 25402 (1992); and Gayle et al., J. Biol. Chem. 268, 7283 (1993).

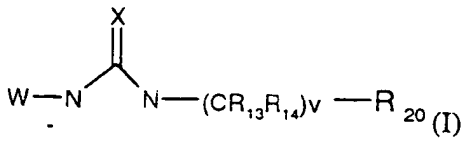
There remains a need for treatment, in this field, for compounds which are capable of binding to the IL-8 α or β receptor. Therefore, conditions associated with an increase in IL-8 production (which is responsible for chemotaxis of neutrophil and T-cells subsets into the inflammatory site) would benefit by compounds which are inhibitors of IL-8 receptor binding.

SUMMARY OF THE INVENTION

This invention provides for a method of treating a chemokine mediated disease, wherein the chemokine is one which binds to an IL-8 α or β receptor and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In particular the chemokine is IL-8.

This invention also relates to a method of inhibiting the binding of IL-8 to its receptors in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

Compounds of Formula (I) useful in the present invention are represented by the structure:



(I)

wherein

X is oxygen or sulfur;

R is $(CR_8R_8)r\ C(O)_2H$, $(CR_8R_8)r\ NH\text{-}C(O)R_a$, $(CR_8R_8)r\ C(O)NR_6'R_7'$, $(CR_8R_8)rNHS(O)_2R_b$, $(CR_8R_8)r\ S(O)_2NHR_c$, $(CR_8R_8)r\ NHC(X_2)NHR_b$, or a tetrazolyl ring;

X_2 is oxygen or sulfur;

R_1 is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted $C_{1\text{-}10}$ alkyl; $C_{1\text{-}10}$ alkyl; $C_{2\text{-}10}$ alkenyl; $C_{1\text{-}10}$ alkoxy; halosubstituted $C_{1\text{-}10}$ alkoxy; azide; $(CR_8R_8)q\ S(O)_tR_4$; hydroxy; hydroxy $C_{1\text{-}4}$alkyl; aryl; aryl $C_{1\text{-}4}$ alkyl; aryloxy; aryl $C_{1\text{-}4}$ alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic, heterocyclic $C_{1\text{-}4}$alkyl; heteroaryl $C_{1\text{-}4}$ alkyloxy; aryl $C_{2\text{-}10}$ alkenyl; heteroaryl $C_{2\text{-}10}$ alkenyl; heterocyclic $C_{2\text{-}10}$ alkenyl; $(CR_8R_8)qNR_4R_5$; $C_{2\text{-}10}$ alkenyl $C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_{10}$; $S(O)_3R_8$; $(CR_8R_8)q\ C(O)R_{11}$; $C_{2\text{-}10}$ alkenyl $C(O)R_{11}$; $C_{2\text{-}10}$ alkenyl $C(O)OR_{11}(CR_8R_8)q\ C(O)OR_{12}$; $(CR_8R_8)q\ OC(O)\ R_{11}$; $(CR_8R_8)qNR_4C(O)R_{11}$; $(CR_8R_8)q\ NHS(O)_2R_{17}$; $(CR_8R_8)q\ S(O)_2NR_4R_5$; or two R_1 moieties together may form $O\text{-}(CH_2)_sO$- or a 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl, and heterocyclic containing moieties may be optionally substituted; provided that there is no ionizable hydrogen having a pKa of 3 to 10 in the 2-position of the phenyl ring;

n is an integer having a value of 1 to 3;

m is an integer having a value of 1 to 3;

q is 0, or an integer having a value of 1 to 10;

r is 0 or an integer of 1 to 4;

s is an integer having a value of 1 to 3;

t is 0, or an integer having a value of 1 or 2;

v is an integer having a value of 1 to 4;

R_4 and R_5 are independently hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C_{1-4}alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O/N/S;

R_6 and R_7 are independently hydrogen or a C_{1-4} alkyl group, or R_6 and R_7 together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;

R_6' and R_7' are independently hydrogen, C_{1-4} alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, heterocyclic C_{2-4}alkenyl moiety, provided that one of R_6' and R_7' is a hydrogen, but not both;

Y is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C_{1-10} alkyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; azide; $(CR_8R_8)q\ S(O)_tR_4$; hydroxy; hydroxyC_{1-4}aikyl; aryl; aryl C_{1-4} alkyl; aryloxy; arylC_{1-4} alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C_{1-4} alkyloxy; heterocyclic, heterocyclic C_{1-4}alkyl; aryl C_{2-10} alkenyl; heteroaryl C_{2-10} alkenyl; heterocyclic C_{2-10} alkenyl; $(CR_8R_8)q\ NR_4R_5$; C_{2-10} alkenyl $C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_{10}$; $S(O)_3R_8$; $(CR_8R_8)q\ C(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)OR_{11}$; $C(O)R_{11}$; $(CR_8R_8)q\ C(O)OR_{12}$; $(CR_8R_8)q\ OC(O)\ R_{11}$; $(CR_8R_8)qNR_4C(O)R_{11}$; $(CR_8R_8)q\ NHS(O)_2R_d$; $(CR_8R_8)q\ S(O)_2NR_4R_5$; or two Y moieties together may form $O\text{-}(CH_2)_sO$- or a 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl, and heterocyclic containing moieties may be optionally substituted;

R_8 is independently selected from hydrogen or C_{1-4} alkyl;

R_{10} is C_{1-10} alkyl $C(O)_2R_8$;

R_{11} is hydrogen, C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC_{1-4}alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC_{1-4}alkyl;

R_{12} is hydrogen, C_{1-10} alkyl, optionally substituted aryl or optionally substituted arylalkyl;

R_{13} and R_{14} are independently hydrogen, optionally substituted C_{1-4} alkyl, or one of R_{13} and R_{14} may be optionally substituted aryl;

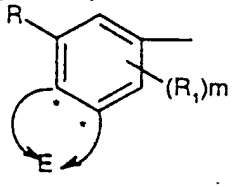
R_{17} is C_{1-4}alkyl, aryl, arylalkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4}alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted;

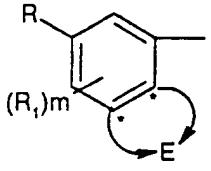
R_a is an alkyl, aryl, aryl C_{1-4}alkyl, heteroaryl, heteroaryl C_{1-4}alkyl, heterocyclic, or a heterocyclic C_{1-4}alkyl moiety, wherein all of these moieties may be optionally substituted;

R_b is a NR_6R_7, alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, heterocyclic C_{2-4}alkenyl moiety, or camphor, wherein all of these moieties may be optionally substituted;

R_c is alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4}alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, or a heterocyclic C_{2-4}alkenyl moiety, wherein all of these moieties may be optionally substituted;

R_d is NR_6R_7, alkyl, arylC_{1-4} alkyl, arylC_{2-4} alkenyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclicC_{1-4} alkyl, wherein the aryl, heteroaryl and heterocyclic containing rings may be optionally substituted;

W is 

, or 

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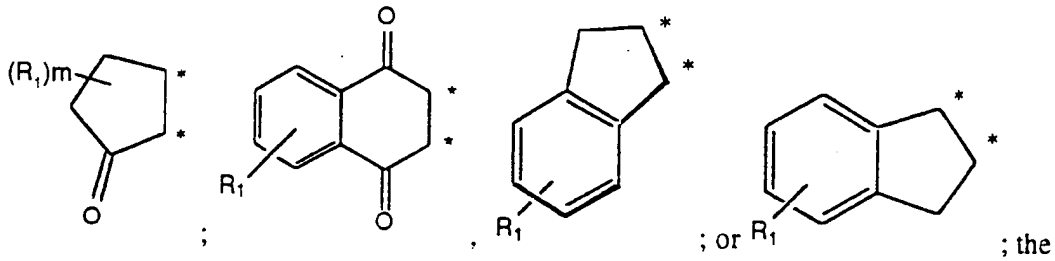
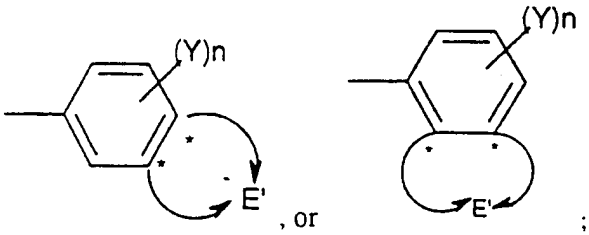
the E containing ring is optionally selected from

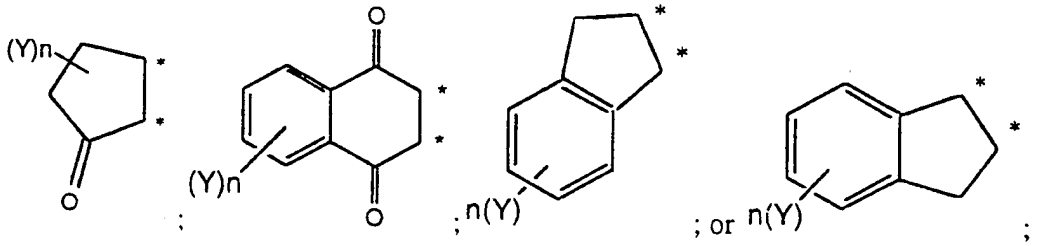


; the asterix * denoting point of attachment of the ring; and

R_{20} is W_1, optionally substituted heteroaryl, optionally substituted C_{5-8} cycloalkyl, optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, or an optionally substituted C_{2-10} alkynyl;

W_1 is 

the E' containing ring is optionally selected from



the asterix * denoting point of attachment of the ring;

or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of IL-8 or other chemokines which bind to the IL-8 α and β receptors. Chemokine mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted herein in the Methods of Treatment section.

In compounds of Formula (I), R is $(CR_8R_8)r\ C(O)_2H$, $(CR_8R_8)r\ NH\text{-}C(O)R_a$, $(CR_8R_8)r\ C(O)NR_6'R_7'$, $(CR_8R_8)rNHS(O)_2R_b$, $(CR_8R_8)r\ S(O)_2NHR_c$, $(CR_8R_8)r\ NHC(X_2)NHR_b$, or a tetrazolyl ring. Each of these moieties may be directly attached to the ring in the 3-position or through the linker $(CR_8R_8)_r$ to the 3-position of the ring.

Suitably, r is 0 or an integer of 1 to 4, preferably 0.

Suitably, X_2 is oxygen or sulfur, preferably oxygen, wherein r is 0 or an integer having a value of 1 to 4.

Suitably, R_6 and R_7 are independently hydrogen or a C_{1-4} alkyl group, or R_6 and R_7 together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur.

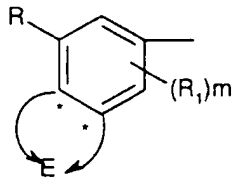
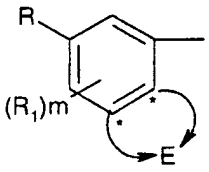
Suitably, $R_{6'}$ and $R_{7'}$ are hydrogen, C_{1-4} alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, or a heterocyclic C_{2-4}alkenyl moiety, provided that one of $R_{6'}$ and $R_{7'}$ are hydrogen, but not both of $R_{6'}$ and $R_{7'}$. All of these moieties may be optionally substituted one to three times independently by halogen; nitro; halosubstituted C_{1-4} alkyl, such as CF_3; C_{1-4} alkyl, such as methyl; C_{1-4} alkoxy, such as methoxy; $NR_9C(O)R_a$; $C(O)NR_6R_7$; $S(O)_3H$; or $C(O)OC_{1-4}$ alkyl.

Suitably R_a is an alkyl, aryl, arylC_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclic, or a heterocyclic C_{1-4}alkyl moiety, wherein all of these moieties may be optionally substituted as defined herein.

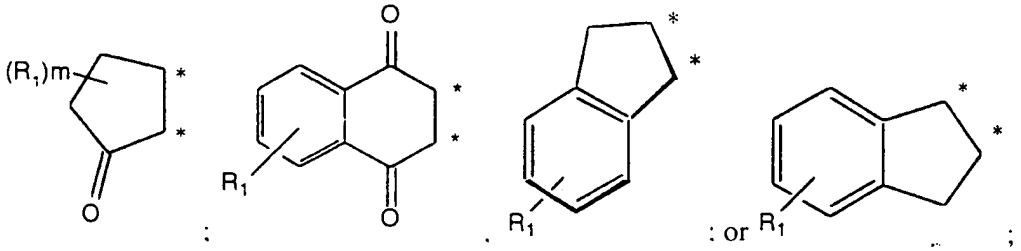
Suitably, R_b is a NR_6R_7, alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, or a heterocyclic C_{2-4}alkenyl moiety, or camphor, wherein the alkyl, aryl, heteroaryl and heterocyclic containing moieties may all be optionally substituted one to three times independently by halogen; nitro; halosubstituted C_{1-4} alkyl, such as CF_3; C_{1-4} alkyl, such as methyl; C_{1-4} alkoxy, such as methoxy; $NR_9C(O)R_a$; $C(O)NR_6R_7$; $S(O)_3H$; or $C(O)OC_{1-4}$ alkyl. R_b is preferably an optionally substituted phenyl, benzyl, or styryl. When R_b is a heteroaryl ring, it is preferably an optionally substituted thiazole, an optionally substituted thienyl, or an optionally substituted quinolinyl ring.

Suitably, R_9 is hydrogen or a C_{1-4} alkyl group, preferably a hydrogen. When R_9 is in the substituent group $NR_9C(O)R_a$, then R_a is preferably an alkyl group, such as methyl.

Suitably R_c is hydrogen, alkyl, aryl, arylC_{1-4}alkyl, arylC_{1-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{1-4}alkenyl, heterocyclic, or heterocyclic C_{1-4}alkyl, or a heterocyclic C_{1-4}alkenyl moiety, all of which may be optionally substituted one to three times independently by halogen, nitro, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} alkoxy, $NR_9C(O)R_a$, $C(O)NR_6R_7$, $S(O)_3H$, or $C(O)OC_{1-4}$ alkyl. Preferably, R_c is an optionally substituted phenyl.

Suitably, W is  , or  .

Suitably, the E containing ring is an optionally substituent which is selected from

 ; wherein the asterix * denotes the point of attachment of the ring.

In compounds of Formula (I), suitably R_1 is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C_{1-10} alkyl, such as CF_3; C_{1-10} alkyl, such as methyl, ethyl, isopropyl, or n-propyl; C_{2-10} alkenyl; C_{1-10} alkoxy, such as methoxy, or ethoxy; halosubstituted C_{1-10} alkoxy, such as trifluoromethoxy; azide; $(CR_8R_8)q\ S(O)_tR_4$; hydroxy; hydroxy C_{1-4}alkyl, such as methanol or ethanol; aryl, such as phenyl or naphthyl; aryl C_{1-4} alkyl, such as benzyl; aryloxy, such as phenoxy; aryl C_{1-4} alkyloxy, such as benzyloxy; heteroaryl; heteroarylalkyl; heteroaryl C_{1-4} alkyloxy; aryl C_{2-10} alkenyl; heteroaryl C_{2-10} alkenyl; heterocyclic C_{2-10} alkenyl; $(CR_8R_8)qNR_4R_5$; C_{2-10} alkenyl $C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_{10}$; $S(O)_3R_8$ such as $S(O)_3H$; $(CR_8R_8)q\ C(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)OR_{11}$; $C(O)R_{11}$; $(CR_8R_8)q\ C(O)OR_{12}$; $(CR_8R_8)qOC(O)R_{11}$; $(CR_8R_8)q\ NR_4C(O)R_{11}$; $(CR_8R_8)q\ NHS(O)_2R_{17}$; $(CR_8R_8)qS(O)_2NR_4R_5$; or two R_1 moieties together may form $O\text{-}(CH_2)_sO$- or a 5 to 6 membered saturated or unsaturated ring. The aryl, heteroaryl, and heterocyclic containing moieties may all be optionally substituted as defined herein below.

Suitable, t is 0, an integer having a value of 1 or 2.

Suitably, s is an integer having a value of 1 to 3.

Suitably, q is 0, or an integer having a value of 1 to 10.

When R_1 forms a dioxybridge, s is preferably 1. When R_1 forms an additional saturated or unsaturated ring, it is preferably a 6 membered ring resulting

in a naphthylene ring system. These saturated and unsaturated ring systems may be optionally substituted independently, 1 to 3 times by the other R_1 moieties as defined above.

Suitably, R_4 and R_5 are independently hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4} alkyl, or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O/N/S.

R_8 is suitably independently selected from hydrogen or C_{1-4} alkyl.

R_{10} is suitably C_{1-10} alkyl $C(O)_2R_8$, such as $CH_2C(O)_2H$ or $CH_2C(O)_2CH_3$.

R_{11} is suitably independently hydrogen, C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4}alkyl, heterocyclic, or heterocyclic C_{1-4}alkyl.

R_{12} is suitably hydrogen, C1-10 alkyl, optionally substituted aryl or optionally substituted arylalkyl.

R_{17} is suitably C_{1-4}alkyl, aryl, arylalkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4}alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted.

Preferably R_1 is halogen, cyano, nitro, CF_3, $C(O)NR_4R_5$, alkenyl $C(O)NR_4R_5$, $C(O)$ R_4R_{10}, alkenyl $C(O)OR_{12}$, heteroaryl, heteroarylalkyl , heteroaryl alkenyl, or $S(O)NR_4R_5$, and preferably R_4 and R_5 are both hydrogen or one of R_4 and R_5 is phenyl. A preferred ring substitution for the R_1 group is in the 4-position of the phenyl ring.

When R is $(CR_8R_8)_r$ OH, $(CR_8R_8)_r$ SH or $(CR_8R_8)_r$ $NHS(O)_2R_b$ than R_1 is preferably substituted in the 4- position, or disubstituted in the 2,4-position. Preferably, the R_1 substituent group is an electron withdrawing moiety, such as nitro, halogen, cyano, trifluoromethyl, or $C(O)NR_4R_5$.

When R is a carboxylic acid, than R_1 is preferably hydrogen, or R_1 is preferably substituted in the 4-position, more preferably substituted by trifluoromethyl or chloro.

In compounds of Formula (I), suitably R_{13} and R_{14} are independently hydrogen, an optionally substituted C_{1-4} alkyl which may be straight or branched as defined herein, or one of R_{13} and R_{14} is an optionally substituted aryl.

When R_{13} or R_{14} are an optionally substituted alkyl, the alkyl moiety may be substituted one to three times independently by halogen: halosubstituted C_{1-4}

alkyl such as trifluoromethyl; hydroxy; hydroxy C_{1-4}alkyl, C_{1-4} alkoxy; such as methoxy, or ethoxy; halosubstituted C_{1-10} alkoxy; $S(O)_tR_4$; aryl; NR_4R_5; $NHC(O)R_4$; $C(O)NR_4R_5$; or $C(O)OR_8$.

Suitably, v is 0 or an integer having a value of 1 to 4.

Suitably, Y is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C_{1-10} alkyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; azide; $(CR_8R_8)q\ S(O)_tR_4$; hydroxy; hydroxyC_{1-4}alkyl; aryl; aryl C_{1-4} alkyl; aryloxy; arylC_{1-4} alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C_{1-4} alkyloxy; heterocyclic, heterocyclic C_{1-4}alkyl; aryl C_{2-10} alkenyl; heteroaryl C_{2-10} alkenyl; heterocyclic C_{2-10} alkenyl; $(CR_8R_8)q\ NR_4R_5$; C_{2-10} alkenyl $C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_{10}$; $S(O)_3H$; $S(O)_3R_8$, such as $S(O)_3H$; $(CR_8R_8)q\ C(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)OR_{11}$; $(CR_8R_8)q\ C(O)OR_{12}$; $(CR_8R_8)q\ OC(O)\ R_{11}$; $(CR_8R_8)q\ NR_4C(O)R_{11}$; $(CR_8R_8)q\ NHS(O)_2R_d$; $(CR_8R_8)q\ S(O)_2NR_4R_5$ or two Y moieties together may form $O\text{-}(CH_2)_sO$- or a 5 to 6 membered saturated or unsaturated ring. The aryl, heteroaryl, and heterocyclic containing moieties may all be optionally substituted.

When Y forms a dioxybridge, s is preferably 1. When Y forms an additional unsaturated ring, it is preferably 6 membered resulting in a naphthylene ring system. These saturated and unsaturated rings may be optionally substituted 1 to 3 times by the other Y moieties as defined above.

Suitably, R_d is a NR_6R_7, alkyl, aryl C_{1-4} alkyl, arylC_{2-4} alkenyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclicC_{1-4} alkyl, or heterocyclic C_{2-4} alkenyl moiety, wherein the aryl, heteroaryl, and heterocyclic containing moieties may all be optionally substituted as defined herein.

Y is preferably a halogen, C_{1-4} alkoxy, optionally substituted aryl, optionally substituted aryloxy or arylalkoxy, methylene dioxy, NR_4R_5, thio C_{1-4}alkyl, thioaryl, halosubstituted alkoxy, optionally substituted C_{1-4} alkyl, or hydroxy alkyl. Y is more preferably a mono-substituted halogen, disubstituted halogen, mono-substituted alkoxy, disubstituted alkoxy, methylenedioxy, aryl, or alkyl. More preferably these groups are mono or di-substituted in the 2'- position or 2'-, 3'-position of the phenyl ring.

While Y may be substituted in any of the 5 ring positions, preferably when R is $(CR_8R_8)rC(O)_2H$, Y is preferably mono-substituted in the 2'-position or 3'-position, with the 4'- preferably being unsubstituted. If the ring is disubstituted, when R is $(CR_8R_8)rC(O)_2H$, substituents are preferably in the 2' or 3' position of a monocyclic ring. While both R_1 and Y can both be hydrogen, it is preferred that at least one of the rings be substituted, and more preferably that both rings are substituted.

In compounds of Formula (I), X is suitably oxygen or sulfur, preferably oxygen.

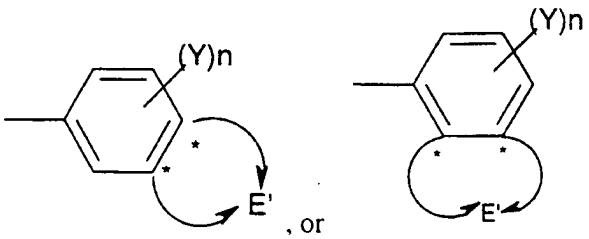
The E and E' rings, denoted by its point of attachment through the asterix (*) may optionally be present. If it is not present the ring is a phenyl moiety which is substituted by the R_1 and Y terms as shown herein. The E and E' ring may be substituted by the R_1 and Y moiety, respectively, in any ring, saturated or unsaturated, and is shown for purposes herein substituted only in the unsaturated ring(s).

In compounds of Formula (I) R_{20} is W_1, an optionally substituted heteroaryl, an optionally substituted C_{5-8} cycloalkyl, an optionally substituted C_{1-10} alkyl, an optionally substituted C_{2-10} alkenyl, or an optionally substituted C_{2-10} alkynyl.

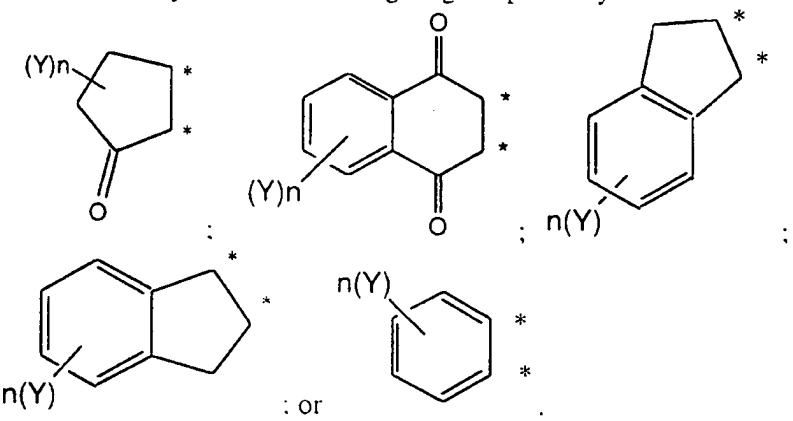
When R_{20} is an optionally substituted C_{5-8} cycloalkyl ring, the ring may be substituted by $(Y)_n$ as defined above.

When R_{20} is an optionally substituted C_{1-10} alkyl, an optionally substituted C_{2-10} alkenyl, or an optionally substituted C_{2-10} alkynyl, these moieties may be optionally substituted one or more times independently by halogen; nitro; cyano; halosubstituted C_{1-10} alkyl, such as trifluoromethyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; $S(O)_tR_4$; hydroxy; hydroxy C_{1-4}alkyl:; aryloxy; arylC_{1-4} alkyloxy; heteroaryloxy; heteroaryl C_{1-4} alkyloxy; heterocyclic, heterocyclic C_{1-4}alkyl; heterocyclicoxy; heterocyclic C_{1-4} alkyloxy; NR_4R_5; $C(O)NR_4R_5$; $C(O)NR_4R_{10}$; $S(O)_3H$; $S(O)_3R_8$; $C(O)R_{11}$; $C(O)OR_{12}$; $OC(O)R_{11}$; or $NR_4C(O)R_{11}$.

When R_{20} is an optionally substituted C_{2-10} alkenyl, or an optionally substituted C_{2-10} alkynyl these moieties may also, in addition to those moieties noted above, be optionally substituted with aryl, aryl C_{1-4} alkyl, heteroaryl, or a heteroaryl C_{1-4} alkyl (and wherein these aryl and heteroaryl containing rings may be optionally substituted).

Suitably, W_1 is  , or

Suitably, the E' containing ring is optionally selected from

 ; or

In compounds of Formula (I), when R_{20} is a heteroaryl (HET) ring, it is suitably a heteroaryl ring or ring system. If the HET moiety is a multi-ring system, the ring containing the heteroatom does not need to be directly attached to the urea moiety or the $(CR_{13}R_{14})_v$ term. All the rings in this ring system may be optionally substituted by the $(Y_{(n)})$ term as defined above. Preferably, the HET moiety is a pyridyl, which may be 2-, 3- or 4-pyridyl. If the ring is a multi system ring it is preferably a benzimidazole, dibenzothiophene, or indole ring. Other heterocyclic rings of interest include, but are not limited to thiophene, furan, pyrimidine, pyrrole, pyrazole, quinoline, isoquinoline, quinazolinyl, pyridine, oxazole, thiazole, thiadiazole, triazole, or imidazole.

R_{20} is preferably an optionally substituted phenyl, allyl, C_{1-10} alkyl, ethoxy carbonyl ethyl, dimethylacetal, 2-methoxy isopropyl, or 2-methoxy ethyl group.

Exemplified compounds of Formula (I) include:

N-(3-Carboxyphenyl)-N'-(2-bromophenyl)urea

N-(3-Carboxymethylphenyl)-N'-(2-bromophenyl)urea

N-(3-Carboxymethylphenyl)-N'-(2,3-dichlorophenyl)urea

N-(3-Carboxyphenyl)-N'-(2,3-dichlorophenyl)urea

N-[3-(2-Carboxyethyl)phenyl]-N'-(2,3-dichlorophenyl) urea
N-(2,4-Dichloro-3-carboxy)-N'-(2-bromophenyl) ureaN-(4-Chloro-3-carboxyphenyl)-N'-(2-bromophenyl)urea
N-(4-Chloro-3-carboxyphenyl) N'-(2,3-dichlorophenyl) urea
N-(4-Chloro-3-carboxyphenyl)-N-(3-chlorophenyl)urea:
or a pharmaceutically acceptable salt thereof.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; $S(O)_{m'}$ C_{1-10} alkyl, wherein m' is 0, 1 or 2, such as methyl thio, methyl sulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR_4R_5 group; $NHC(O)R_4$; $C(O)NR_4R_5$; C(O)OH; $S(O)_2NR_4R_5$; $NHS(O)_2R_2$, C_{1-10} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted C_{1-10} alkyl, such CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, optionally substituted heterocylic, optionally substituted heterocylicalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, and wherein these aryl , heteroaryl, or heterocyclic moieties may be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C_{1-10} alkoxy; $S(O)_{m'}C_{1-10}$ alkyl; amino, mono & di- C_{1-4} alkyl substituted amino, such as in the NR_4R_5 group; C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl, such as CF_3.

R_2 is suitably C_{1-4} alkyl, aryl, aryl C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4}alkyl.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The following terms, as used herein, refer to:

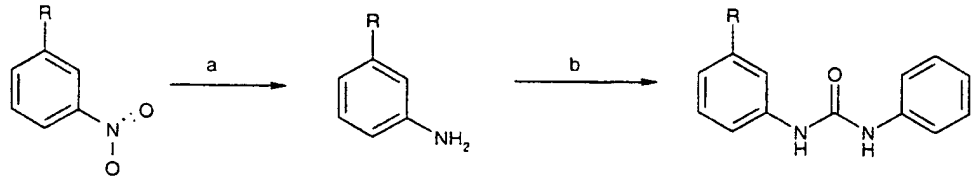
- "halo" - all halogens, that is chloro, fluoro, bromo and iodo.
- "C_{1-10}alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
- "heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, or imidazolidine.
- "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C_{1-10} alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.
- "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized $S(O)_2$ moiety.
- the term "wherein two R_1 moieties (or two Y moieties) may together form a 5 or 6 membered saturated or unsaturated ring" is used herein to mean the formation of a napthylene ring system or a phenyl moiety having attached a 6 membered partially unsaturated ring such as a C_6 cycloalkenyl, i.e. hexene, or a C_5 cycloalkenyl moiety, such as a cyclopentene ring.

Methods of Preparation

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for in these Schemes is applicable for the producing compounds of Formula (I) having a variety of different R, R_1, and aryl groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. Once the urea nucleus has been established, further compounds of these formulas may be prepared by applying standard techniques for functional group interconversion, well known in the art. While the schemes are shown with W and R_{20} as phenyl this is merely for illustration purposes only.

The desired aniline 2-scheme-1 can be synthesized by the reduction of the corresponding nitro if it is not available commercially. This reduction can be accomplished by a number of reducing agents such as hydrogen and catalytic Palladium on carbon or tin chloride in a polar solvent such as DMF or ethyl acetate. This aniline (2-scheme 1) can then be condensed with a commercially available isocyanate in an aprotic solvent such as DMF, DMSO or toluene.

Scheme 1



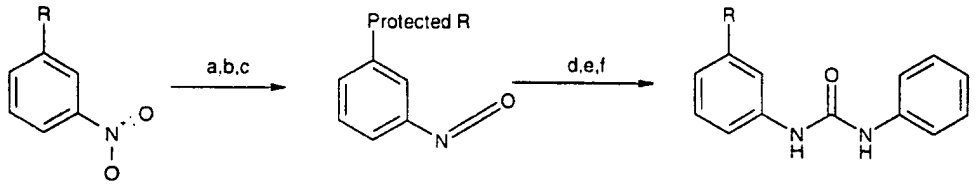
1 2 3

R=CH_2CH_2COOH, COOH, CH_2COOH

a)H_2, Pd/C b)PhCNO

Alternately, the desired compound could synthesized by the protection of the carboxylic acid by conditions well known in art, such as diazomethane to form the methyl ester. This compound could then be reduced by a number of reducing agents such as hydrogen and catalytic Palladium on carbon or tin chloride in a polar solvent such as DMF or ethyl acetate. Condensation with a phosgene equivalent such as di- or triphosgene in the presence of a base such as triethyl amine or bicarbonate would form the isocyanate 4-scheme-2. This compound could then be reacted with the desired commercially available aniline. The carboxylic acid could then be deprotected by conditions standard in the art, such as metal hydroxide in a polar

solvent such as THF/water, then acidified with an acid such as HCl to form 3, scheme 2.



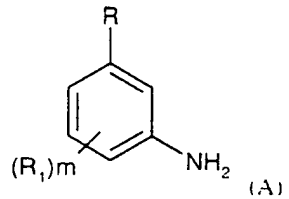
1 4 3

R=CH_2CH_2COOH, COOH, or CH_2COOH; Protected R wherein R=CH_2CH_2COOMe, COOMe, or CH_2COOMe

a) CH_2N_2, ether b) H_2,5%Pd/C c) triphosgene, Et_3N d) $PhNH_2$.DMF e) LiOH, THF/H_2O f) HCl/H_2O

Pharmaceutically acceptable salts of compounds of Formula (I) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid or base in the presence of a suitable solvent.

Another aspect of the present invention is the analogous process for producing a compound of Formula (I) which process comprises reacting a compound of the formula



(A)

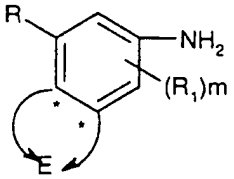
wherein R, R_1 and m are as defined for Formula (I),

with a compound of the formula:

$$-N(X)-(CR_{13}R_{14})_v-R_{20}$$

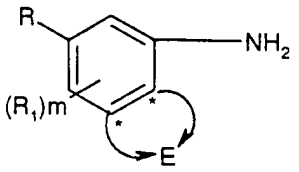
wherein X, R_{13}, R_{14}, v and R_{20} are as defined in Formula (I) to yield a compound of Formula (I).

Alternatively, a compound of Formula (A1)



wherein E, R, R_1 and m are as defined for Formula (I), or

a compound of Formula (A2)



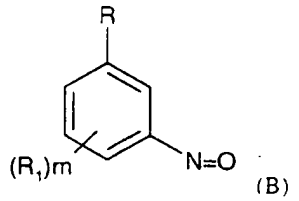
wherein E, R, R_1 and m are as defined for Formula (I), or

may instead be reacted with a compound of the formula:

$$-N(X)-(CR_{13}R_{14})_v - R_{20};$$

wherein X, R_{13}, R_{14}, v and R_{20} are as defined in Formula (I) to yield a compound of Formula (I).

Another aspect of the present invention is the alternative process for producing a compound of Formula (I) which process comprises reacting a compound of the formula:



(B)

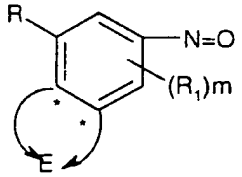
wherein R_1, m and R are as defined for formula (I);

with a compound of the formula:

$$NH_2-(CR_{13}R_{14})_v - R_{20};$$

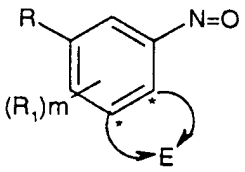
wherein R_{13}, R_{14}, v and R_{20} are as defined in Formula (I) to yield a compound of Formula (I); and deprotecting the R group if necessary.

As above, one may alternatively use a compound of Formula (B1)



wherein E, R, R_1 and m are as defined for Formula (I), or

a compound of Formula (B2)



wherein E, R, R_1 and m are as defined for Formula (I), or

may instead be reacted with a compound of the formula:

$$NH_2\text{-}(CR_{13}R_{14})_v - R_{20};$$

wherein R_{13}, R_{14}, v and R_{20} are as defined in Formula (I) to yield a compound of Formula (I); and deprotecting the R group if necessary.

In the Examples, all temperatures are in degrees Centigrade (°C). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated. ^{1}H-NMR (hereinafter "NMR") spectra were recorded at 250 MHz or 400MHz using a Bruker AM 250 or Am 400 spectrometer, respectively. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, equiv. indicates the proportion of a molar equivalent of reagent relative to the principal reactant.

Flash chromatography is run over Merck Silica gel 60 (230 - 400 mesh).

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents used herein are of the highest available purity and all reactions are run under anhydrous conditions in an argon atmosphere unless otherwise indicated.

Example 1

Preparation of N-(3-Carboxyphenyl)-N'-(2-bromophenyl)urea

A solution of 3-amino benzoic acid (1 equivalent (hereinafter "eq"), 1.37 gram (hereinafter "g")) in DMF was treated with 2-bromo phenyl isocyanate (1 eq, 1.98 g) at about 80°C for about 2 hours. The solution was cooled and the product was purified by recrystalization from methylene chloride and hexanes to afford 1.28g of the titled compound as white solid. MS(ES)M-H=333

Example 2

Preparation of N-(3-Carboxymethylphenyl)-N'-(2-bromophenyl)urea

A solution of 3-amino phenyl acetic acid (1eq, .151 g) in DMF was treated with 2-bromo phenyl isocyanate (1 eq, .198 g) at about 80 °C for about 2 hours. The solution was cooled and the product was purified by recrystalization from methylene chloride and hexanes to afford 0.32g of the titled compound as white solid. MS(ES)M-H=347

Example 3

Preparation of N-(3-Carboxymethylphenyl)-N'-(2,3-dichlorophenyl)urea

A solution of 3-amino phenyl acetic acid (1eq, 151 milligrams (hereinafter "mg")) in DMF was treated with 2,3-dichloro phenyl isocyanate (1 eq, 188 mg) at 80 °C for 2 hours. The solution was cooled and the product was purified by recrystalization from methylene chloride and hexanes to afford .12 g of the titled compound as white solid. MS(ES)M-H=337

Example 4

Preparation of N-(3-Carboxyphenyl)-N'-(2,3-dichlorophenyl)urea

A solution of 3-amino benzoic acid (1 eq, 1.37 g) in DMF was treated with 2,3-dichloro phenyl isocyanate (1 eq, 1.88 g) at 80 °C for 2 hours. The solution was cooled and the product was purified by recrystalization from methylene chloride and hexanes to afford 1.01 g of the titled compound as white solid. MS(ES)M-H=323

Example 5

Preparation of N-[3-(2-Carboxyethyl)phenyl]-N'-(2,3-dichlorophenyl) urea

a) 3-amino dihydrocinnamic acid

A solution of 3-nitro dihydrocinnamic acid (500 mg) in ethyl acetate was treated with 10%Pd/C (500 mg). The resulting suspension was flushed with hydrogen and allowed to stir overnight at room temperature. The reaction mixture was purged with argon and then filtered through celite. The filtrate was concentrated and the residue was recrystallized from toluene and ethyl acetate. ^1H NMR (DMSO) 6.95 t (1H), 6.4 m (3 H), 2.7 t (2H), 2.45 t (2H)

b) N-[3-(2-carboxyethyl)phenyl]-N'-(2,3-dichlorophenyl) urea

A solution of 3-amino dihydro cinnamic acid (1 eq, 83 mg) in DMF was treated with 2,3-dichloro phenyl isocyanate (1 eq, 94 mg) at 80 °C for 2 hours. The solution was cooled and the product was purified by recrystalization from methylene chloride and hexanes to afford 0.037g of the titled compound as white solid. ^1H

NMR (DMSO) 9.45 s (1H), 8.47 s (1H), 8.17 d (1H), 7.31 m (4H), 7.24 t (1H), 6.88 d (1H), 2.73 t (2H), 2.54 t (2H)

Example 6

Preparation of N-(2,4-Dichloro-3-carboxy)-N'-(2-bromophenyl) urea

a) 5-amino 2,6-dichloro benzoic acid

A solution of 5-nitro-2,6-dichloro benzoic acid (2.0 g) in ethyl acetate was treated with 10% Pd/C(1.5g). The suspension was flushed with hydrogen and allowed to stir at room temperature overnight. The reaction mixture was purged with argon and filtered through celite. The filtrate was concentrated and the residue was purified by recrystalization from ethyl acetate and hexanes to afford the title compound (0.7g) as a white solid. ^{1}H NMR (DMSO) 7.15 d (1H), 6.8 d (1H), 5.74 s (1H, br)

b) N-(2,4-Dichloro-3-carboxy)-N'-(2-bromophenyl) urea

A solution of 5-amino-2,6-dichloro benzoic acid (1 eq, 250 mg) in DMF was treated with 2-bromo phenyl isocyanate (1 eq, 153 uL) at 80 ^{o}C for 2 hours. The solution was cooled and the product was purified by recrystalization from methylene chloride and hexanes to afford 35 mg of the titled compound as white solid. MS(ES)M-H=401

Example 7

Preparation of N-(4-Chloro-3-carboxyphenyl)-N'-(2-bromophenyl)urea

A solution of 5-amino-2-chloro benzoic acid (1 eq, 1.71 g) in DMF was treated with 2-bromo phenyl isocyanate (1 eq, 1.98 g) at 80 ^{o}C for 2 hours. The solution was cooled and the product was purified by recrystalization from methylene chloride and hexanes to afford 0.880 g of the titled compound as white solid. MS(ES)M-H=367

Example 8

Preparation of N-(4-Chloro-3-carboxyphenyl) N'-(2,3-dichlorophenyl) urea

A solution of 5-amino-2-chloro benzoic acid (1 eq, 1.71 g) in DMF was treated with 2,3-dichloro phenyl isocyanate (1 eq, 1.88 g) at 80 ^{o}C for 2 hours. The solution was cooled and the product was purified by recrystalization from methylene chloride and hexanes to afford 1.57g of the titled compound as white solid. MS(ES)M-H=357

Example 9

Preparation of N-(4-Chloro-3-carboxyphenyl)-N-(3-chlorophenyl)urea

A solution of 5-amino-2-chloro benzoic acid (1 eq, 1.71 g) in DMF was treated with 3-chloro phenyl isocyanate (1 eq, 1.53 g) at 80 °C for 2 hours. The solution was cooled and the product was purified by recrystalization from methylene chloride and hexanes to afford 0.66g of the titled compound as white solid. MS(ES)M-H=323

METHOD OF TREATMENT

The compounds of Formula (I), or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated IL-8 cytokine production by such mammal's cell, such as but not limited to monocytes and/or macrophages, or other chemokines which bind to the IL-8 α or β receptor, also referred to as the type I or type II receptor.

Accordingly, the present invention provides a method of treating a chemokine mediated disease, wherein the chemokine is one which binds to an IL-8 α or β receptor and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In particular, the chemokines are IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78.

The compounds of Formula (I) are administered in an amount sufficient to inhibit cytokine function, in particular IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78, such that they are biologically regulated down to normal levels of physiological function, or in some case to subnormal levels, so as to ameliorate the disease state. Abnormal levels of IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 for instance in the context of the present invention, constitute: (i) levels of free IL-8 greater than or equal to 1 picogram per mL; (ii) any cell associated IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 above normal physiological levels; or (iii) the presence IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 above basal levels in cells or tissues in IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 respectively, is produced.

There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. Chemokine mediated diseases include psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, stroke, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, cardiac and renal reperfusion

injury, glomerulonephritis, thrombosis, graft vs. host reaction, Alzheimer's disease, allograft rejections, malaria, restinosis, angiogenesis or undesired hematopoietic stem cells release, rhinovirus infections, and various bone resorptive indications, such as osteoporosis or osteoarthritis.

The association of interleukin-8 and rhinovirus may be found in articles such as: Turner.et al., Clin. Infect. Dis. (1998), 26(4), 840-846; Sanders, et al., J. Virol. (1998), 72(2), 934-942; Sethi, et al., Clin. Exp. Immunol. (1997), 110(3), 362-369; Zhu, et al., Am. J. Physiol. (1997), 273(4, Pt. 1), L814-L824; Terajima, et al., Am. J. Physiol. (1997), 273(4, Pt. 1), L749-L759; Grunberg, et al., Clin. Exp. Allergy (1997), 27(1), 36-45; and Johnston, et al., J. Infect. Dis. (1997), 175(2), 323-329.

The association of interleukin-8 and osteoporosis may be found in articles such as: Streckfus et al., J. Gerontol., Ser. A (1997), 52A(6), M343-M351; Hermann, T. WO 95/31722; and Chaudhary, et al., Endocrinology (Baltimore) (1992), 130(5), 2528-34.

These diseases are primarily characterized by massive neutrophil infiltration, T-cell infiltration, or neovascular growth, and are associated with increased IL-8, GROα, GROβ, GROγ or NAP-2 production which is responsible for the chemotaxis of neutrophils into the inflammatory site or the directional growth of endothelial cells. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8, GROα, GROβ, GROγ or NAP-2 has the unique property of promoting neutrophil chemotaxis, enzyme release including but not limited to elastase release as well as superoxide production and activation. The α-chemokines but particularly, GROα, GROβ, GROγ or NAP-2, working through the IL-8 type I or II receptor can promote the neovascularization of tumors by promoting the directional growth of endothelial cells. Therefore, the inhibition of IL-8 induced chemotaxis or activation would lead to a direct reduction in the neutrophil infiltration.

Recent evidence also implicates the role of chemokines in the treatment of HIV infections, Littleman et al., Nature 381, pp 661 (1996) and Koup et al., Nature 381, pp 667 (1996).

The present invention also provides for a means of treating, in an acute setting, as well as preventing, in those individuals deemed susceptible to, CNS injuries by the chemokine receptor antagonist compounds of Formula (I).

CNS injuries as defined herein include both open or penetrating head trauma, such as by surgery, or a closed head trauma injury, such as by an injury to the head region. Also included within this definition is ischemic stroke, particularly to the brain area.

Ischemic stroke may be defined as a focal neurologic disorder that results from insufficient blood supply to a particular brain area, usually as a consequence of an embolus, thrombi, or local atheromatous closure of the blood vessel. The role of inflammatory cytokines in this are has been emerging and the present invention provides a mean for the potential treatment of these injuries. Relatively little treatment, for an acute injury such as these has been available.

Present evidence also indicates the use of IL-8 inhibitors in the treatment of atherosclerosis. The first reference, Boisvert et al., J Clin Invest, 1998, 101:353-363 shows, through bone marrow transplantation, that the absence of IL-8 receptors on stem cells (and, therefore, on monocytes/macrophages) leads to a reduction in the development of atherosclerotic plaques in LDL receptor deficient mice. Additional supporting references are: Apostolopoulos et al., Arterioscler Thromb Vasc Biol. 1996, 16:1007-1012; Liu et al., Arterioscler Thromb Vasc Biol, 1997, 17:317-323; Rus et al., Atherosclerosis. 1996, 127:263-271.; Wang et al., J Biol Chem. 1996, 271:8837-8842; Yue et al., Eur J Pharmacol. 1993, 240:81-84; Koch et al., Am J Pathol. 1993, 142:1423-1431.; Lee et al., Immunol Lett. 1996, 53, 109-113.; and Terkeltaub et al., Arterioscler Thromb. 1994, 14:47-53.

TNF-α is a cytokine with proinflammatory actions, including endothelial leukocyte adhesion molecule expression. Leukocytes infiltrate into ischemic brain lesions and hence compounds which inhibit or decrease levels of TNF would be useful for treatment of ischemic brain injury. See Liu et al., Stoke, Vol. 25., No. 7, pp 1481-88 (1994) whose disclosure is incorporated herein by reference.

Models of closed head injuries and treatment with mixed 5-LO/CO agents is discussed in Shohami et al., J. of Vaisc & Clinical Physiology and Pharmacology, Vol. 3. No. 2, pp. 99-107 (1992) whose disclosure is incorporated herein by reference. Treatment which reduced edema formation was found to improve functional outcome in those animals treated.

The compounds of Formula (I) are administered in an amount sufficient to inhibit IL-8, binding to the IL-8 alpha or beta receptors, from binding to these receptors, such as evidenced by a reduction in neutrophil chemotaxis and activation. The discovery that the compounds of Formula (I) are inhibitors of IL-8 binding is based upon the effects of the compounds of Formulas (I) in the *in vitro* receptor binding assays which are described herein. The compounds of Formula (I) have been shown, in some instances, to be dual inhibitors of both recombinant type I and type II IL-8 receptors. Preferably the compounds are inhibitors of only one receptor, more preferably Type II.

As used herein, the term "IL-8 mediated disease or disease state" refers to any and all disease states in which IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 plays a role, either by production of IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 themselves, or by IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 causing another monokine to be released, such as but not limited to IL-1, IL-6 or TNF. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to IL-8, would therefore be considered a disease stated mediated by IL-8.

As used herein, the term "chemokine mediated disease or disease state" refers to any and all disease states in which a chemokine which binds to an IL-8 α or β receptor plays a role, such as but not limited IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78. This would include a disease state in which, IL-8 plays a role, either by production of IL-8 itself, or by IL-8 causing another monokine to be released, such as but not limited to IL-1, IL-6 or TNF. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to IL-8, would therefore be considered a disease stated mediated by IL-8.

As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF-α) and Tumor Necrosis Factor beta (TNF-ß).

As used herein, the term "chemokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response, similar to the term "cytokine" above. A chemokine is primarily secreted through cell transmembranes and causes chemotaxis and activation of specific white blood cells and leukocytes, neutrophils, monocytes, macrophages, T-cells, B-cells, endothelial cells and smooth muscle cells. Examples of chemokines include, but are not limited to, IL-8, GRO-α, GRO-β, GRO-γ, NAP-2, ENA-78, IP-10, MIP-1α, MIP-β, PF4, and MCP 1, 2, and 3.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of Formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of Formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I)

externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the Formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the Formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active

agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100 ^{o}C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of Formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of Formula (I), the daily oral dosage regimen will preferably be from about 0.01 to about 80 mg/kg of total body weight. The daily parenteral dosage regimen about 0.001 to about 80 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

BIOLOGICAL EXAMPLES

The IL-8, and GRO-α chemokine inhibitory effects of compounds of the present invention were determined by the following *in vitro* assay:

Receptor Binding Assays:

[^{125}I] IL-8 (human recombinant) was obtained from Amersham Corp., Arlington Heights, IL. with specific activity 2000 Ci/mmol. GRO-α was obtained from NEN- New England Nuclear. All other chemicals were of analytical grade. High levels of recombinant human IL-8 type α and β receptors were individually expressed in Chinese hamster ovary cells as described previously (Holmes, *et al.*, *Science*, **1991**, *253*, 1278). The Chinese hamster ovary membranes were homogenized according to a previously described protocol (Haour, *et al.*, *J Biol Chem.*, 249 pp 2195-2205 (1974)). Except that the homogenization buffer was changed to 10mM Tris-HCL, 1mM MgS04, 0.5mM EDTA (ethylene-diaminetetra-acetic acid), 1mMPMSF (α-toluenesulphonyl fluoride), 0.5 mg/L Leupeptin, pH 7.5. Membrane protein concentration was determined using Pierce Co. micro-assay kit using bovine serum albumin as a standard. All assays were performed in a 96-well micro plate format. Each reaction mixture contained ^{125}I IL-8 (0.25 nM) or ^{125}I Gro-α and 0.5 µg/mL of IL-8Rα or 1.0 µg/mL of IL-8Rβ membranes in 20 mM Bis-Trispropane and 0.4 mM Tris HCl buffers, pH 8.0, containing 1.2 mM $MgSO_4$, 0.1 mM EDTA, 25 mM NaCl and 0.03% CHAPS. In addition, drug or compound of interest was added which had been pre-dissolved in DMSO so as to reach a final concentration of between 0.01nM and 100 uM. The assay was initiated by addition of ^{125}I-IL-8. After 1 hour at room temperature the plate was harvested using a Tomtec 96-well harvester onto a glass fiber filtermat blocked with 1% polyethylenimine/0.5% BSA and washed 3 times with 25 mM NaCl, 10 mM TrisHCl, 1 mM $MgSO_4$, 0.5 mM EDTA, 0.03 % CHAPS, pH 7.4. The filter was then dried and counted on the Betaplate liquid scintillation counter. The recombinant IL-8 Rα, or Type I. receptor is also referred to herein as the non-permissive receptor and the recombinant IL-8 Rβ, or Type II. receptor is referred to as the permissive receptor.

All of the exemplified compounds of Formulas (I) noted herein in the Synthetic Chemistry Section, Example 1 to 9, demonstrated inhibitory in the permissive models for IL-8 receptor inhibition. The following compounds were found to be inactive in this assay: N-(2,4-Dichloro-3-carboxy)-N'-(2,3-

dichlorophenyl)urea N-(3-Carboxyphenyl)-N'-(phenyl)urea and N-(3-Methylcarboxyphenyl)-N'-(phenyl)urea.

Chemotaxis Assay :

The *in vitro* inhibitory properties of these compounds are determined in the neutrophil chemotaxis assay as described in Current Protocols in Immunology, vol. I, Suppl 1, Unit 6.12.3., whose disclosure is incorporated herein by reference in its entirety. Neutrophils where isolated from human blood as described in Current Protocols in Immunology Vol. I. Suppl 1 Unit 7.23.1, whose disclosure is incorporated herein by reference in its entirety. The chemoattractants IL-8, GRO-α, GRO-β, GRO-γ and NAP-2 are placed in the bottom chamber of a 48 multiwell chamber (Neuro Probe, Cabin John, MD) at a concentration between 0.1 and 100 nM. The two chambers are separated by a 5um polycarbonate filter. When compounds of this invention are tested, they are mixed with the cells (0.001 - 1000 nM) just prior to the addition of the cells to the upper chamber. Incubation is allowed to proceed for between about 45 and 90 min. at about 37°C in a humidified incubator with 5% CO_2. At the end of the incubation period, the polycarbonate membrane is removed and the top side washed, the membrane then stained using the Diff Quick staining protocol (Baxter Products, McGaw Park, IL, USA). Cells which have chemotaxed to the chemokine are visually counted using a microscope. Generally, four fields are counted for each sample, these numbers are averaged to give the average number of cells which had migrated. Each sample is tested in triplicate and each compound repeated at least four times. To certain cells (positive control cells) no compound is added, these cells represent the maximum chemotactic response of the cells. In the case where a negative control (unstimulated) is desired, no chemokine is added to the bottom chamber. The difference between the positive control and the negative control represents the chemotactic activity of the cells.

Elastase Release Assay:

The compounds of this invention are tested for their ability to prevent Elastase release from human neutrophils. Neutrophils are isolated from human blood as described in Current Protocols in Immunology Vol. I, Suppl 1 Unit 7.23.1. PMNs 0.88 x 10^6 cells suspended in Ringer's Solution (NaCl 118, KCl 4.56, NaHCO3 25, KH2PO4 1.03, Glucose 11.1, HEPES 5 mM, pH 7.4) are placed in each well of a 96 well plate in a volume of 50 ul. To this plate is added the test compound (0.001 - 1000 nM) in a volume of 50 ul, Cytochalasin B in a volume of

50 ul (20ug/ml) and Ringers buffer in a volume of 50 ul. These cells are allowed to warm (37 °C, 5% CO2, 95% RH) for 5 min. before IL-8, GROα, GROβ, GROγ or NAP-2 at a final concentration of 0.01 - 1000 nM was added. The reaction is allowed to proceed for 45 min. before the 96 well plate is centrifuged (800 xg 5 min.) and 100 ul of the supernatant removed. This supernatant is added to a second 96 well plate followed by an artificial elastase substrate (MeOSuc-Ala-Ala-Pro-Val-AMC, Nova Biochem. La Jolla, CA) to a final concentration of 6 ug/ml dissolved in phosphate buffered saline. Immediately, the plate is placed in a fluorescent 96 well plate reader (Cytofluor 2350, Millipore, Bedford, MA) and data collected at 3 min. intervals according to the method of Nakajima et al J. Biol. Chem. 254 4027 (1979). The amount of Elastase released from the PMNs is calculated by measuring the rate of MeOSuc-Ala-Ala-Pro-Val-AMC degradation.

TNF-α in Traumatic Brain Injury Assay

This assay provides for examination of the expression of tumor necrosis factor mRNA in specific brain regions which follow experimentally induced lateral fluid-percussion traumatic brain injury (TBI) in rats. Since TNF- α is able to induce nerve growth factor (NGF) and stimulate the release of other cytokines from activated astrocytes, this post-traumatic alteration in gene expression of TNF- α plays an important role in both the acute and regenerative response to CNS trauma. A suitable assay may be found in WO 97/35856 or WO 97/49286 whose disclosures are incorporated herein by reference.

CNS Injury model for IL-β mRNA

This assay characterizes the regional expression of interleukin-1ß (IL-1ß) mRNA in specific brain regions following experimental lateral fluid-percussion traumatic brain injury (TBI) in rats. Results from these assays indicate that following TBI, the temporal expression of IL-1ß mRNA is regionally stimulated in specific brain regions. These regional changes in cytokines, such as IL-1ß play a role in the post-traumatic pathologic or regenerative sequelae of brain injury. A suitable assay may be found in WO 97/35856 or WO 97/49286 whose disclosures are incorporated herein by reference.

***In vivo* - Athereoschlerosis assay:**

In vivo models for measuring atherosclerosis in mice is based on the assay of Paigen et al with small modifications as described below. See Paigen B, Morrow A, Holmes PA, Mitchell D, Williams RA. Quantitative assessment of atherosclerotic lesions in mice. *Atherosclerosis* 68: 231-240 (1987); and Groot PHE, van Vlijmen BJM, Benson GM, Hofker MH, Schiffelers R, Vidgeon-Hart M, Havekes LM. Quantitative assessment of aortic atherosclerosis in APOE*3 Leiden transgenic mice and its relationship to serum cholesterol exposure. *Arterioscler Thromb Vasc Biol.* 16: 926-933 (1996).

Sectioning and staining of the aortic sinus

Cross-sections of the aortic root are taken as has been described previously (1,2). Briefly, the hearts are bisected just below the level of the atria and the base of the heart plus aortic root are taken for analysis. After equilibrating the tissue in OCT compound overnight the hearts are immersed in OCT compound on a cryostat chuck (Bright Instrument Company Ltd., UK) with the aorta facing the chuck. The tissue is frozen by surrounding the chuck with dry ice. The hearts are then sectioned perpendicular to the axis of the aorta, starting within the heart and working in the direction of the aorta. Once the aortic root has been identified by the appearance of the three valve leaflets, alternate 10 mm sections are taken and mounted on gelatinised slides. Sections are air dried for 1 hour and subsequently rinsed briefly in 60% isopropyl alcohol. The sections are stained with Oil Red O, counterstained with Mayer's haematoxylin, cover slipped using glycerol gelatin and sealed with nail varnish.

Quantification of atherosclerosis in the aortic root

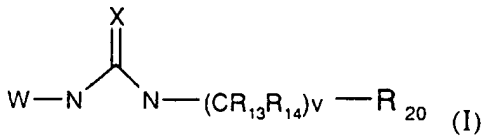
Ten alternate sections of the aortic root are imaged using an Olympus BH-2 microscope equipped with an 4x objective and a video camera (Hitachi, HV-C10). Twenty-four bit colour images are acquired and analyzed using a PC (Datacell Pentium P5-133, Datacell, Berks, U.K.) fitted with a framegrabbing board (Snapper, Active Imaging Ltd, Berks, U.K.) and running Optimas software (version 5.1, Optimas Corp., WA, U.S.A.). The images are captured under identical lighting, microscope, camera and PC conditions. Quantification of the atherosclerotic lesion areas is performed by drawing around the lesions by hand using the Optimas software. Colour thresholds are set that quantify the areas that are stained red within the lesions. Absolute values for the cross-sectional areas of the lesions and the areas stained red are obtained by calibrating the software using an image of the grid on a haemocytometer slide.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the arc can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed is:

1. A method of treating a chemokine mediated disease state, wherein the chemokine binds to an IL-8 α or β receptor in a mammal, which comprises administering to said mammal an effective amount of a compound of the formula:



(I)

wherein

X is oxygen or sulfur;

R is $(CR_8R_8)r\ C(O)_2H$, $(CR_8R_8)r\ NH\text{-}C(O)R_a$, $(CR_8R_8)r\ C(O)NR_6'R_7'$, $(CR_8R_8)r\ NHS(O)_2R_b$, $(CR_8R_8)r\ S(O)_2NHR_c$, $(CR_8R_8)r\ NHC(X_2)NHR_b$, or a tetrazolyl ring;

X_2 is oxygen or sulfur;

R_1 is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C_{1-10} alkyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; $(CR_8R_8)q\ S(O)_tR_4$; hydroxy; hydroxy C_{1-4}alkyl; aryl; aryl C_{1-4} alkyl; aryloxy; aryl C_{1-4} alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic, heterocyclic C_{1-4}alkyl; heteroaryl C_{1-4} alkyloxy; aryl C_{2-10} alkenyl; heteroaryl C_{2-10} alkenyl; heterocyclic C_{2-10} alkenyl; $(CR_8R_8)qNR_4R_5$; C_{2-10} alkenyl $C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_{10}$; $S(O)_3R_8$; $(CR_8R_8)q\ C(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)OR_{11}(CR_8R_8)q\ C(O)OR_{12}$; $(CR_8R_8)q\ OC(O)\ R_{11}$; $(CR_8R_8)qNR_4C(O)R_{11}$; $(CR_8R_8)q\ NHS(O)_2R_{17}$; $(CR_8R_8)q\ S(O)_2NR_4R_5$; or two R_1 moieties together may form $O\text{-}(CH_2)_sO$- or a 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl, and heterocyclic containing moieties may be optionally substituted;

n is an integer having a value of 1 to 3;

m is an integer having a value of 1 to 3;

q is 0, or an integer having a value of 1 to 10;

r is 0, or an integer having a value of 1 to 4;

s is an integer having a value of 1 to 3;

t is 0, or an integer having a value of 1 or 2;

v is an integer having a value of 1 to 4;

R4 and R5 are independently hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C_{1-4}alkyl, heterocyclic, or heterocyclic C_{1-4} alkyl, or R4 and R5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O/N/S;

R6 and R7 are independently hydrogen or a C_{1-4} alkyl group, or R6 and R7 together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;

R6' and R7' are independently hydrogen, C_{1-4} alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, heterocyclic C_{2-4}alkenyl moiety, provided that one of R6' and R7' are hydrogen, but not both;

Y is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C_{1-10} alkyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; azide; $(CR_8R_8)_q S(O)_t R_4$; hydroxy; hydroxyC_{1-4}alkyl; aryl; aryl C_{1-4} alkyl; aryloxy; arylC_{1-4} alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C_{1-4} alkyloxy; heterocyclic, heterocyclic C_{1-4}alkyl; aryl C_{2-10} alkenyl; heteroaryl C_{2-10} alkenyl; heterocyclic C_{2-10} alkenyl; $(CR_8R_8)_q NR_4R_5$; C_{2-10} alkenyl $C(O)NR_4R_5$; $(CR_8R_8)_q C(O)NR_4R_5$; $(CR_8R_8)_q C(O)NR_4R_{10}$; $S(O)_3H$; $S(O)_3R_8$; $(CR_8R_8)_q C(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)OR_{11}$; $C(O)R_{11}$; $(CR_8R_8)_q C(O)OR_{12}$; $(CR_8R_8)_q OC(O) R_{11}$; $(CR_8R_8)_q NR_4C(O)R_{11}$; $(CR_8R_8)_q NHS(O)_2R_d$; $(CR_8R_8)_q S(O)_2NR_4R_5$; or two Y moieties together may form $O\text{-}(CH_2)_sO$- or a 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl, and heterocyclic containing moieties may be optionally substituted;

R8 is independently selected from hydrogen or C_{1-4} alkyl;

R_{10} is C_{1-10} alkyl $C(O)_2R_8$;

R_{11} is hydrogen, C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC_{1-4}alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC_{1-4}alkyl;

R_{12} is hydrogen, C_{1-10} alkyl, optionally substituted aryl or optionally substituted arylalkyl;

R_{13} and R_{14} are independently hydrogen, optionally substituted C_{1-4} alkyl, or one of R_{13} and R_{14} may be optionally substituted aryl;

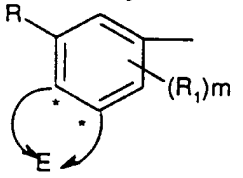
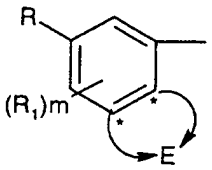
R_{17} is C_{1-4}alkyl, aryl, arylalkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4}alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted;

R_a is an alkyl, aryl, aryl C_{1-4}alkyl, heteroaryl, heteroaryl C_{1-4}alkyl, heterocyclic, or a heterocyclic C_{1-4}alkyl moiety, wherein all of these moieties may be optionally substituted;

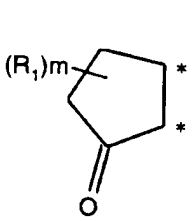
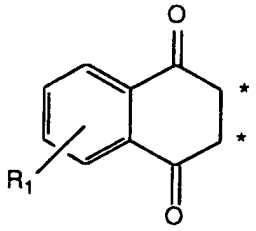
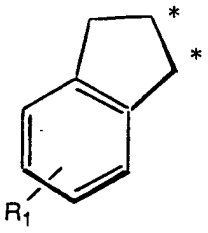
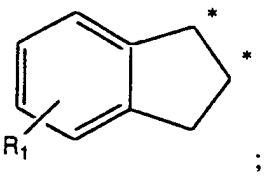
R_b is a NR_6R_7, alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, heterocyclic C_{2-4}alkenyl moiety, or camphor, wherein all of these moieties may be optionally substituted;

R_c is alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4}alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, or a heterocyclic C_{2-4}alkenyl moiety, all of which may be optionally substituted one to three times independently by halogen, nitro, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} alkoxy, $NR_9C(O)R_a$, $C(O)NR_6R_7$, $S(O)_3H$, or $C(O)OC_{1-4}$ alkyl;

R_d is NR_6R_7, alkyl, arylC_{1-4} alkyl, arylC_{2-4} alkenyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, or heterocyclicC_{1-4} alkyl, wherein the aryl, heteroaryl and heterocyclic containing moieties may all be optionally substituted;

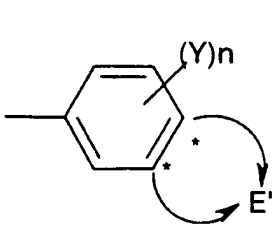
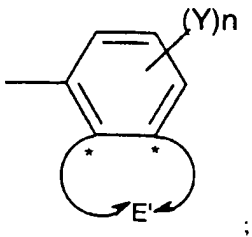
W is  , or  ;

the E containing ring is optionally selected from

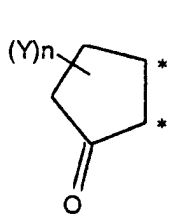
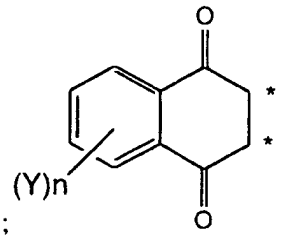
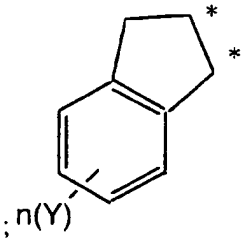
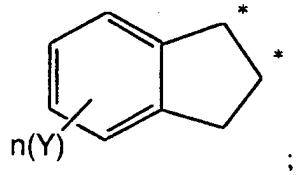
 ;  ,  ; or  ;

the asterix * denoting point of attachment of the ring;

R_{20} is W_1, optionally substituted heteroaryl, optionally substituted C_{5-8} cycloalkyl, optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, or an optionally substituted C_{2-10} alkynyl;

W_1 is  , or  ;

the E' containing ring is optionally selected from

 ;  ;  ; or  ;

the asterix * denoting point of attachment of the ring;

or a pharmaceutically acceptable salt thereof.

2. The method according to Claim 1 wherein the R is $(CR_8R_8)rC(O)_2H$.

3. The method according to Claim 1 wherein R_1 is halogen, cyano, nitro, CF_3, $C(O)NR_4R_5$, alkenyl $C(O)NR_4R_5$, $C(O)$ R_4R_{10}, alkenyl $C(O)OR_{12}$, heteroaryl, heteroarylalkyl , heteroaryl alkenyl, or $S(O)NR_4R_5$.

4. The method according to Claim 1 wherein R_{20} is W_1.

5. The method according to Claim 1 wherein R_{20} is heteroaryl.

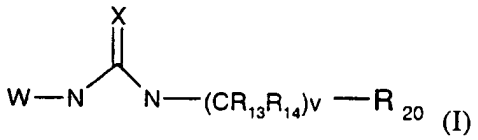
6. The method according to Claim 4 wherein Y is halogen, C_{1-4} alkoxy, optionally substituted aryl, optionally substituted arylalkoxy, methylene dioxy, NR_4R_5, thioC_{1-4}alkyl, thioaryl, halosubstituted alkoxy, optionally substituted C_{1-4}alkyl, hydroxy alkyl.

7. The method according to Claim 1 wherein R_1 is mono substituted in the 2- or 4- position, or di-substituted in the 2,4- position by an electron withdrawing moiety.

8. The method according to any of Claims 1 to 7 wherein the chemokine mediated disease selected from psoriasis, or atopic dermatitis, asthma, chronic

obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, atheroschlerosis, bone resorption diseases, Alzheimer's disease, graft vs. host reaction, or allograft rejections.

9. A compound of the formula:



(I)

wherein

X is oxygen or sulfur;

R is $(CR_8R_8)r\ C(O)_2H$, $(CR_8R_8)r\ NH\text{-}C(O)R_a$, $(CR_8R_8)r\ C(O)NR_6'R_7'$, $(CR_8R_8)_rNHS(O)_2R_b$, $(CR_8R_8)r\ S(O)_2NHR_c$, $(CR_8R_8)r\ NHC(X_2)NHR_b$, or a tetrazolyl;

X_2 is oxygen or sulfur;

R_1 is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted $C_{1\text{-}10}$ alkyl; $C_{1\text{-}10}$ alkyl; $C_{2\text{-}10}$ alkenyl; $C_{1\text{-}10}$ alkoxy; halosubstituted $C_{1\text{-}10}$ alkoxy; azide; $(CR_8R_8)q\ S(O)_tR_4$; hydroxy; hydroxy $C_{1\text{-}4}$alkyl; aryl; aryl $C_{1\text{-}4}$ alkyl; aryloxy; aryl $C_{1\text{-}4}$ alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic, heterocyclic $C_{1\text{-}4}$alkyl; heteroaryl $C_{1\text{-}4}$ alkyloxy; aryl $C_{2\text{-}10}$ alkenyl; heteroaryl $C_{2\text{-}10}$ alkenyl; heterocyclic $C_{2\text{-}10}$ alkenyl; $(CR_8R_8)qNR_4R_5$; $C_{2\text{-}10}$ alkenyl $C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_{10}$; $S(O)_3R_8$; $(CR_8R_8)q\ C(O)R_{11}$; $C_{2\text{-}10}$ alkenyl $C(O)R_{11}$; $C_{2\text{-}10}$ alkenyl $C(O)OR_{11}(CR_8R_8)q\ C(O)OR_{12}$; $(CR_8R_8)q\ OC(O)R_{11}$; $(CR_8R_8)qNR_4C(O)R_{11}$; $(CR_8R_8)q\ NHS(O)_2R_{17}$; $(CR_8R_8)q\ S(O)_2NR_4R_5$; or two R_1 moieties together may form $O\text{-}(CH_2)_sO$- or a 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl, and heterocyclic containing moieties may be optionally substituted;

n is an integer having a value of 1 to 3;

m is an integer having a value of 1 to 3;

q is 0, or an integer having a value of 1 to 10;

r is 0 or an integer of 1 to 4;

s is an integer having a value of 1 to 3;

t is 0, or an integer having a value of 1 or 2;

v is an integer having a value of 1 to 4;

R_4 and R_5 are independently hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C_{1-4}alkyl, heterocyclic, or heterocyclic C_{1-4} alkyl, or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O/N/S;

$R_{6'}$ and $R_{7'}$ are independently hydrogen, C_{1-4} alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, or heterocyclic C_{2-4}alkenyl moiety, provided that one of $R_{6'}$ and $R_{7'}$ are hydrogen, but not both;

R_6 and R_7 are independently hydrogen or a C_{1-4} alkyl group, or R_6 and R_7 together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;

Y is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C_{1-10} alkyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; azide; $(CR_8R_8)q\ S(O)_tR_4$; hydroxy; hydroxyC_{1-4}alkyl; aryl; aryl C_{1-4} alkyl; aryloxy; arylC_{1-4} alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C_{1-4} alkyloxy; heterocyclic, heterocyclic C_{1-4}alkyl; aryl C_{2-10} alkenyl; heteroaryl C_{2-10} alkenyl; heterocyclic C_{2-10} alkenyl; $(CR_8R_8)q\ NR_4R_5$; C_{2-10} alkenyl $C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_{10}$; $S(O)_3R_8$; $(CR_8R_8)q\ C(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)OR_{11}$; $C(O)R_{11}$; $(CR_8R_8)q\ C(O)OR_{12}$; $(CR_8R_8)q\ OC(O)\ R_{11}$; $(CR_8R_8)q\ NR_4C(O)R_{11}$; $(CR_8R_8)q\ NHS(O)_2R_d$; $(CR_8R_8)q\ S(O)_2NR_4R_5$; or two Y moieties together may form $O\text{-}(CH_2)_sO$- or a 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl, and heterocyclic containing moieties may be optionally substituted;

R_8 is independently selected from hydrogen or C_{1-4} alkyl;

R_{10} is C_{1-10} alkyl $C(O)_2R_8$;

R_{11} is hydrogen, C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC_{1-4}alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC_{1-4}alkyl;

R_{12} is hydrogen, C_{1-10} alkyl, optionally substituted aryl or optionally substituted arylalkyl;

R_{13} and R_{14} are independently hydrogen, optionally substituted C_{1-4} alkyl, or one of R_{13} and R_{14} may be optionally substituted aryl;

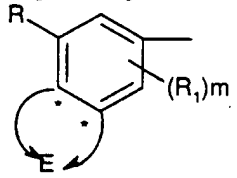
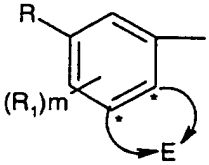
R_{17} is C_{1-4}alkyl, aryl, arylalkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4}alkyl, wherein the aryl, heteroaryl and heterocyclic rings may all be optionally substituted;

R_a is an alkyl, aryl, aryl C_{1-4}alkyl, heteroaryl, heteroaryl C_{1-4}alkyl, heterocyclic, or a heterocyclic C_{1-4}alkyl moiety, wherein all of these moieties may be optionally substituted;

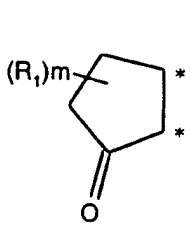
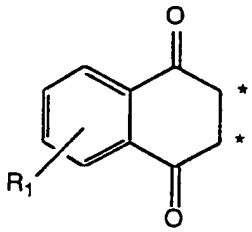
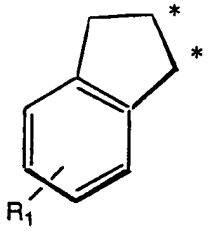
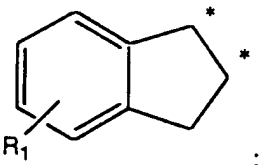
R_b is a NR_6R_7, alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, heterocyclic C_{2-4}alkenyl moiety, or camphor, wherein all of these moieties may be optionally substituted:

R_c is alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4}alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, or a heterocyclic C_{2-4}alkenyl moiety, all of which may be optionally substituted one to three times independently by halogen, nitro, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} alkoxy, $NR_9C(O)R_a$, $C(O)NR_6R_7$, $S(O)_3H$, or $C(O)OC_{1-4}$ alkyl;

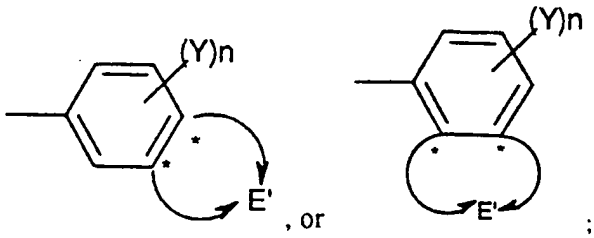
R_d is NR_6R_7, alkyl, arylC_{1-4} alkyl, arylC_{2-4} alkenyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, or heterocyclicC_{1-4} alkyl, wherein the aryl, heteroaryl and heterocyclic containing moieties may all be optionally substituted;

W is  , or  ;

the E containing ring is optionally selected from

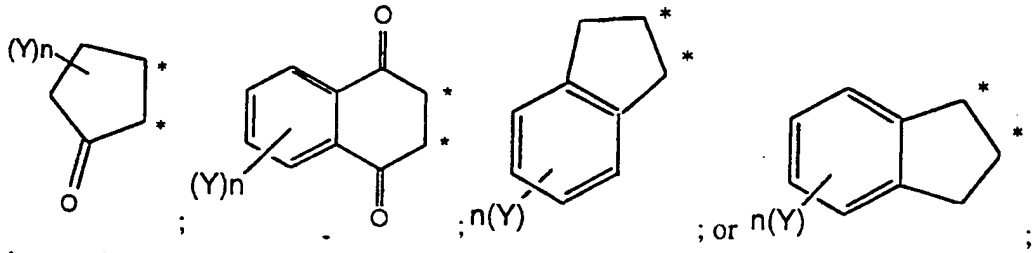
 ;  ,  ; or  ; the asterix * denoting point of attachment of the ring;

R_{20} is W_1, optionally substituted heteroaryl, optionally substituted C_{5-8} cycloalkyl, optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, or an optionally substituted C_{2-10} alkynyl;

W_1 is 

, or ;

the E' containing ring is optionally selected from



; ; ; ; or ;

the asterix * denoting point of attachment of the ring;
or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 9 wherein the R is $(CR_8R_8)rC(O)_2H$.

11. The compound according to Claim 9 wherein R_1 is halogen, cyano, nitro, CF_3, $C(O)NR_4R_5$, alkenyl $C(O)NR_4R_5$, $C(O)$ R_4R_{10}, alkenyl $C(O)OR_{12}$, heteroaryl, heteroarylalkyl, heteroaryl alkenyl, or $S(O)NR_4R_5$.

12. The compound according to Claim 9 wherein R_{20} is W_1.

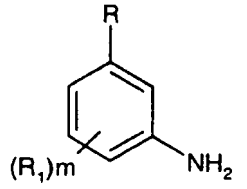
13. The compound according to Claim 9 wherein R_{20} is heteroaryl.

14 The compound according to Claim 12 wherein Y is halogen, C_{1-4} alkoxy, optionally substituted aryl, optionally substituted arylalkoxy, methylene dioxy, NR_4R_5, thioC_{1-4}alkyl, thioaryl, halosubstituted alkoxy, optionally substituted C_{1-4}alkyl, or hydroxy alkyl.

15. The compound according to Claim 9 wherein R_1 is mono substituted in the 2- or 4- position, or disubstituted in the 2-4- position by an electron withdrawing moiety.

16. A pharmaceutical composition comprising an effective amount of a compound according to any of Claims 9 to 15, and a pharmaceutically acceptable carrier or diluent.

17. A process for producing a compound according to Claim 9 which process comprises reacting a compound of the formula



(A)

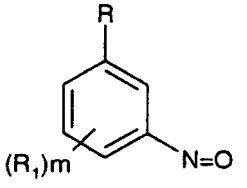
wherein R, R_1 and m are as defined for Formula (I),

with a compound of the formula:

$-N(X)-(CR_{13}R_{14})_v - R_{20}$;

wherein X, R_{13}, R_{14}, v and R_{20} are as defined in Formula (I) to yield a compound of Formula (I).

18. A process for producing a compound of Formula (I) which process comprises reacting a compound of the formula:



(B)

wherein R_1, m and R are as defined for formula (I);

with a compound of the formula:

$NH_2-(CR_{13}R_{14})_v - R_{20}$;

wherein R_{13}, R_{14}, v and R_{20} are as defined in Formula (I) to yield a compound of Formula (I); and deprotecting the R group if necessary.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/15830

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : CO7C 241/00
US CL :562/439

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 562/439

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS ON STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database CAPLUS on STN, Acc. No. 1996:643902, WIDDOWSON et al., 'Preparation of N,N'-diphenylurea derivatives as interleukin-8 receptor antagonists,' abstract, WO 9625157 A1, 22 August 1996.	1-18
Y, P	US 5,780,483 A (WIDDOWSON ET AL) 14 July 1998 (14/07/98), see entire document.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

28 SEPTEMBER 1998

Date of mailing of the international search report

27 OCT 1998

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